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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/616,365	07/08/2003	Peter T.W. Cheng	LA0089 NP	2318

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EXAMINER	
JOHNSEN, JASON H	
ART UNIT	**PAPER NUMBER**
1623	

DATE MAILED: 10/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/616,365	CHENG ET AL.	
	Examiner	Art Unit	
	Jason H. Johnsen	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *17-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-10 and 14-16* is/are rejected.

7)☐ Claim(s) *11-13* is/are objected to.

8)☐ Claim(s) *1-19* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *N/A* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/10/04;10/31/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

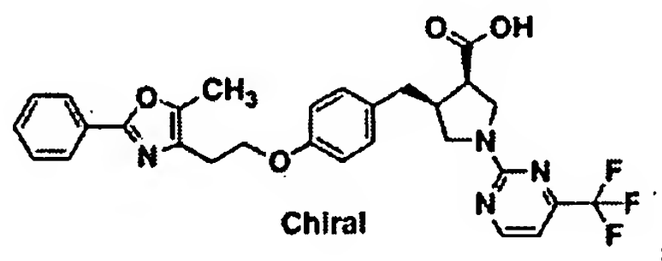
The information disclosure statementS (IDS) submitted on 03/10/2004 and 10/31/2003 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the examiner is considering the information disclosure statements.

Specification

The abstract of the disclosure is objected to because it contains more than 25 lines. Correction is required. See MPEP § 608.01(b).

Election/Restrictions

The Markush groups set forth in the claims include both independent and distinct inventions, and patentably distinct compounds (or species) within each invention. However, this application discloses and claims a plurality of patentably distinct inventions far too numerous to list individually. Moreover, each of these inventions contains a plurality of patentably distinct compounds, also far too numerous to list individually. For these reasons provided below, restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-16 (in part), drawn to compounds, compositions and a method of use wherein the ring defined by X_2-X_6 is defined in Example 170 

, Q is C, X is CH, X^5 is 0, E, and Z^1 and Z^2 are carbon, classified in class 548 subclass 215.

II. Claims 1-16(in part), drawn to compounds, compositions not contained in Group I, classified in various subclasses of class 544, 546, and 548 depending on the variables. **NOTE:** If group II is elected, further restriction will be required.

III. Claims 17-19 drawn to a pharmaceutical combination comprising a compound as defined in claim 1 and a second agent, classified in various subclasses of 544, 546, and 548 depending on the variables.

Rationale Establishing Patentable Distinctiveness Within Each Group

Each Invention Set listed above is directed to or involves the use or making of compounds which are recognized in the art as being distinct from one another because of their diverse chemical structure, their different chemical properties, modes of action, different effects and reactive conditions (MPEP 806.04, MPEP 808.01). Additionally, the level of skill in the art is not such that one invention would be obvious over either of the other inventions, i.e. they are patentable over each other. Chemical structures which are similar are presumed to function similarly, whereas chemical structures that are not similar are not presumed to function similarly. The presumption even for similar chemical structures though is not irrebuttable, but may be overcome by scientific reasoning or evidence showing that the structure of the prior art would not have been expected to function as the structure of the claimed invention. Note that in accordance with the holdings of Application of Papesch, 50 CCPA 1084, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and In re Lalu, 223 USPQ 1257 (Fed. Cir. 1984), chemical structures are patentably distinct where the structures are either not structurally similar, or the prior art fails to suggest a function of a claimed compound would have been expected from a similar structure.

The above Groups represent general areas wherein the inventions are independent and distinct, each from the other because of the following reasons:

Groups I-III are directed to distinct compounds that are classified in different classes. The inventions of Groups I-III are separate and patentably distinct because there is no patentable co-action among them and a reference anticipating one member will not render another obvious. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter and different classification, a search of the two groups designated above would impose an undue burden upon the examiner, and restriction for examination purposes is indicated proper. Applicant's claims embrace an extremely broad and diverse group of compounds and compositions classified in a myriad of classifications. The ring defined by X_2-X_6 has a high degree of variability, as does the ring containing Z, Z^1, E, and E^2. The rings not only differ in number and identity of each atom in the ring, but also differ as to size of each ring. Therefore, it is almost impossible to capture the variability of the core structure in a number of groups. Group I is built around applicant's preferred species election, Example 170 in the specification.

A telephone interview was conducted on August 31, 2005 with attorney of record Burton Rodney, in which a provisional election of group I with traverse was obtained. Therefore, the application will be examined commensurate in scope with this election. Claims 17-19 have been withdrawn from consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, and 14-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The following reason(s) apply:

Regarding the compounds and compositions of these claims

The nature of the invention in the instant application has claims that embrace a diversity of chemically and physically distinct compounds, wherein the core structure is substituted by R^3. While several compounds are disclosed, there is insufficient guidance for preparing all of the compounds embraced by the full scope of these claims, specifically, where R^3 can be arylalkyl broadly, arylcarbonyl broadly, heteroaryl broadly, heteroarylcarbonyl broadly, etc.; the full scope of which is found on page 527 of the claims.

Furthermore, all compounds embraced by this broad scope have not been tested using the in vitro assays described in the specification. There is no data to support a conclusion of their effectiveness in treating diabetes, or any other blood glucose, triglyceride, insulin or NEFA modulating disease. Examples should be of sufficient scope as to justify the scope of the claim. However, the generic claims are much broader in scope than is represented by the testing. The definitions of the various R^3 variables on the substituted heterocyclic ring system embrace many structurally divergent groups not represented at all in testing, since testing for the instant compounds is not seen in the specification. Markush claims must be provided with support in the disclosure when the "working examples" fail to include written description(s) which teach

how to make and use Markush members embraced thereby in full, clear and exact terms. See *In re Fouch, 169 USPQ 429.*

This area of activity can be expected to be highly structure specific and unpredictable, as is generally true for chemically based pharmacological activity. In view of the structural divergence in the claims, one skilled in the art could not reasonably extrapolate the activities of some of the claimed compounds to the other structurally divergent compounds which are being used for their physiological activity, the scope of the claims must have a reasonable correlation to the scope of enablement provided by the specification. *See In re Surrey 151 USPQ 724* regarding sufficiency of disclosure for a Markush group. No reasonable assurance has been made that the instant compounds as an entire class have the required activities needed to practice the invention, e.g. treat diabetes and related diseases or the treatment of malignant lesions, IBS, Crohn's disease, and proliferative diseases. Thus, factors such as "sufficient working examples," "the level of skill in the art," and "predictability in the art" have been demonstrated to be sufficiently lacking in the instant case for the scope being claimed.

Regarding the methods of use found in claims 15 and 16

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims without undue experimentation. The instant disclosure is not seen to be sufficient to enable the use of compounds of the formula in claim 1 to treat all of the diseases or disorders in claims 15 and 16 without undue experimentation.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in ***In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400,***

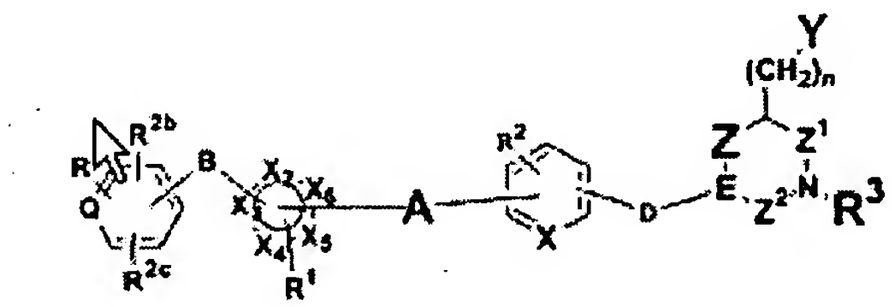
1404 (Fed. Cir. 1988). A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

The breadth of the instant claims are extremely broad due to the large number of diseases and disorders which could potentially be treated by the compounds of the formula



, including inflammation, "diabetic complications" early malignant lesions generally, premalignant lesions generally, epithelial tumors generally, proliferative diseases, etc. Applicant has not provided sufficient evidence to support a claim drawn to all of this disorders or diseases.

The nature of the invention

Claim 15 and 16 are directed to a compound for the treatment of a number of diseases or disorders including allergies, congestion, hypotension, cardiovascular disease, sleeping

disorders, obesity, disturbances of the central nervous system, migraines, etc., by administering a compound or composition of claim 1.

The state of the prior art

The state of the prior art concerning many of the broad diseases listed in Claims 15 and 16 are complex and unpredictable. For example, inflammation generally. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages which have stuck tightly

together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammatory disorders generally.

Similar arguments about breadth of causes, mechanisms and treatments, or lack thereof, can be made for other diseases listed in these claims, such as "diabetic complications," malignant lesions generally, premalignant lesions generally, and proliferative diseases, which encompasses many disorders, including cancer generally. For example, there never has been a compound capable of treating cancer generally. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective

against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs Novo Nordisk*, 42 USPQ2nd 1001, 1006.

The level of one of ordinary skill

The level of skill in the art is high, that of a M.D. or PhD.

The level of predictability in the art

The instant claimed invention is highly unpredictable. Due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity. There is no absolute predictability even in view of the seemingly high level of

skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. In re Fisher, 427 F. 2d, 833, 166 USPQ 18 (CCPA 1970), indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Hence, in the absence of a showing of a nexis between the binding affinity of the compounds of the formula of claim 1 and the corresponding efficacy of treating a wide variety of disorders listed in claim 15 and 16, one of skill in the art is unable to fully predict possible results from the administration of the compound of the formula due to the unpredictability of the art pertaining to disorders responsive to these heterocyclic derivatives.

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance, which would allow the skilled artisan to extrapolate from the disclosure and examples provided, to use the claimed method commensurate in the scope with the instant claims. Applicant provides limited guidance regarding the use of the instant compound in treating a wide variety of disorders each of which have complex etiologies. Applicant does not provide any biological activity of the compounds of instant invention. The data and evidence, or lack thereof, provided in the instant disclosure leads the examiner to doubt the objective truth of assertions of treatment of the disorders listed in claims 15 and 16.

The existence of working examples

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without

undue experimentation. In re Wright, 999 F. 2d 1557, 1562; 27 USPQ 2d 1510, 1514 (Fed. Cir. 1993). Applicant does not establish a fact based, evidentiary link between the compounds and compositions of claim and biological activity to treat any diseases.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

As discussed above, based on the unpredictable nature of the invention, the state of the prior art, and the extreme breadth of the claims, one skilled in the art could not use the claimed invention without undue experimentation.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Regarding claims 15 and 16, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Objections

Claims 6-10, and 13 are objected to because of the following informalities:

1. Claim 6 and 7 do not contain a period, nor do they have “and” before the last representative moiety. Additionally, Claim 6 and 7 should contain “is selected from one of the following…” or similar phrasing after the word “is.”

2. Claim 8 should contain commas between each formula, as well as the phrase “selected from the group consisting of...” or similar phrasing expressing the same idea before the group of formulas. Additionally, claim 8 lacks a period.

3. Claim 9 and 10 contain a period in the middle of the claim.

4. Claim 13 does not have a period nor does it have commas between each compound. Also, claim 13 should have a phrase such as "selected from the group consisting of...." before the first compound. Additionally, the word "and" should appear before the last representative compound. Appropriate correction is required.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jason H. Johnsen** whose telephone number is **571-272-3106**. The examiner can normally be reached on Mon-Friday, 8:30-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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